# Synthesis of the Nucleoside Antibiotic Formycin B

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Summary Curtius rearrangement of the 4-azide of 5-(tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole-3,4-dicarboxylic acid gave the *N*-carboxy-anhydride of the 4-amino-3-acid the methyl ester of which, on heating in formamide followed by catalytic hydrogenolysis, gave formycin B.
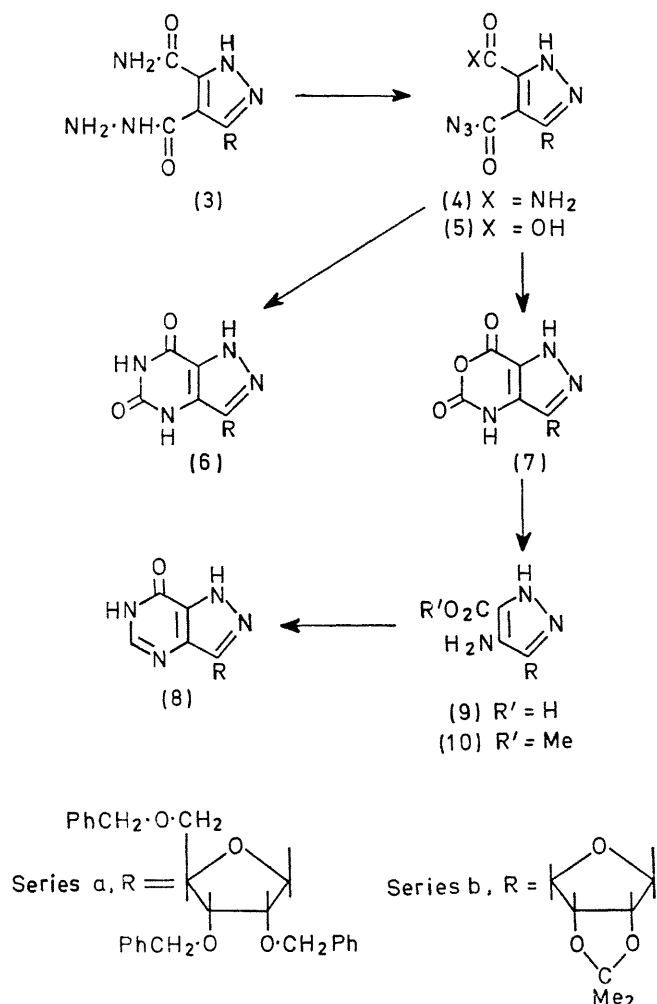
Recent communications[1-3] have elaborated a promising synthetic approach to the *C*-nucleoside formycin B (**1**), but so far only the metabolite, oxoformycin B (**2**), has been synthesized. We now report the successful synthesis of formycin B.

A key intermediate in this general approach is the pyrazole *C*-nucleoside (**3a**), a 3-ribosyl tri-*O*-benzyl ether with the two pyrazole carboxy-groups selectivity functionalized as the 4-hydrazinocarbonyl-3-carboxamide. Previously,[3]

(1)

(2)
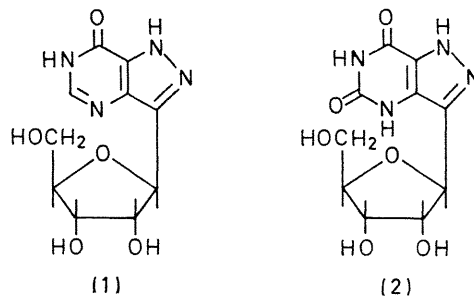
the azide (**4a**), formed from (**3a**), gave, by a Curtius rearrangement, the dione (**6a**), the tri-*O*-benzyl derivative of

oxoformycin B. Similar treatment of analogous 4-azidocarbonyl-3-carboxamides[1,4] as models for (4a) also gave the corresponding diones, exclusively. Presumably in each case the intermediate pyrazole-4-isocyanate cyclized readily with the adjacent 3-carboxamide group. This reaction could not be adjusted, except in the simplest model series,[1] to give

(3)

(4) X = NH₂
(5) X = OH

(6)

(7)

(8)

(9) R' = H
(10) R' = Me

Series a, R =

Series b, R =

(11) X = NAc

(12) X = NCONH₂   R = CH₂Ph

(13)

pyrazole-4-amines (or derivatives thereof) which were required for synthesis of pyrazolo[4,3-d]pyrimidine-7-ones [e.g., (1) and (8)], in the formamide-cyclization method of Robins.[5]

This obstacle has now been surmounted by treating (3a), m.p. 120—122°, in acetic acid–carbon tetrachloride at 3° with dinitrogen tetroxide in the presence of sodium acetate, thereby generating the 4-azide (5a) with an adjacent carboxy-group at C-3, i.r., 3·7—3·8 br (OH) and 4·59 and 4·67 (N₃) μm. Curtius rearrangement of (5a) by heating in toluene solution at 100° then afforded the N-carboxylic anhydride (7a), i.r. 5·53 and 5·70 (C=O) μm, probably by cyclization of the intermediate isocyanate. These intermediates (5a) and (7a) were obtained as glasses, characterized by spectral comparison with (5b) and (7b). Ring opening of the anhydride occurred in tetrahydrofuran–water

(5:1) under reflux, with loss of the i.r. bands at 5·53 and 5·70 μm, to give the 4-amino-3-acid (9a). *Treatment of* (9a) with 2,2-dimethoxypropane and hydrochloric acid afforded the ester (10a), purified by chromatography on silica gel in CHCl₃ [25% yield based on (3a)], 5·80 (C=O) and 3·0 and 6·17 (NH₂) μm, τ (CDCl₃; internal Me₄Si) 4·77 (d, 1'-H) and 6·12 (s, CO₂Me). Heating of (10a) in formamide at 218° (bath) for 1·75 h afforded 2',3',5'-tri-O-benzylformycin B (8a), purified chromatographically (silica gel; ethyl acetate–benzene, 1:1) and crystallized (40% yield) from MeOH–H₂O (2:1), m.p. 145—146°, τ 2·08 (s, 5-H) and 4·35 (d, 1'-H). Hydrogenolytic debenzylation with palladium chloride[6] in ethanol afforded formycin B (1), m.p. 245—249° (from ethanol) without depression on admixture with an authentic sample of the natural product, chromatographically identical, Rf 0·55 (silica gel; CHCl₃–MeOH, 1:1), λmax (pH 1) 276 nm (ε 8318), (pH 13) 290 (9134).

This useful reaction sequence (5) → (10) was first explored in the model series (series b) previously described,[2] with 2,3-O-isopropylidene-β-DL-erythrofuranose as the sugar portion, where crystalline intermediates could be expected. The hydrazido-carboxamide (3b), treated as for (3a), afforded the azido-acid (5b) (66%), m.p. 137—139° (from CHCl₃–CCl₄), i.r. 3·7br (OH), 4·61 and 4·68 (N₃) μm. The N-carboxylic anhydride (7b) crystallized from the hot toluene of the Curtius reaction medium (90%), m.p. 200—210° (decomp.), i.r. 5·52 and 5·71 (C=O) μm. Hydrolysis of (7b) in hot water afforded an amino-acid as expected, but rather surprisingly a pH of 2·5 was attained in the solution and the 2',3'-O-isopropylidene group was lost. The blocked amino-ester (10b) was therefore obtained by esterification of (5b) with diazomethane to an unstable azido-ester, which was heated with aqueous hydrogen carbonate solution to complete the Curtius rearrangement and accomplish the hydrolysis to (10b), m.p. 134—135°, τ 6·10 (s, CO₂Me). Heating (10b) in formamide gave the 7-one (8b), m.p.
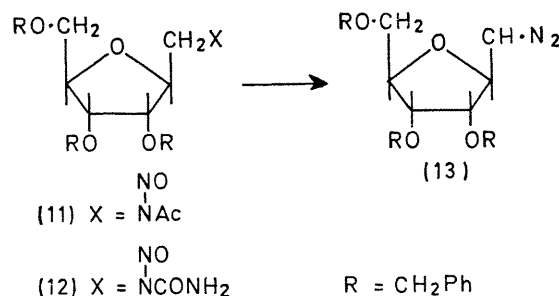
245—253° (from water), λmax (pH 1) 273 nm (ε 7000), (pH 13) 290 (7610).

If (3b) was treated more conventionally with aqueous nitrous acid in a two-phase system with ether to give the azide (4b), the Curtius rearrangement under various conditions then afforded only the 5,7-dione (6b), m.p. 305—307° (decomp.), λmax (pH 1) 286 nm (ε 5480), (pH 13) 304 (4450).

The pyrazole C-nucleoside intermediates were synthesized from 1-diazo-sugars in 1,3-dipolar additions[2,3] with dimethyl acetylenedicarboxylate. The diazo-ether (13) was generated from the nitroso-acetamide (11) in preference to the

nitroso-urea[3] (12), since the latter was unavoidably contaminated with an isocyanate, presumably formed *via* nitrosation of the terminal nitrogen of the urea.

We thank Chemotherapy, the National Cancer Institute, the National Institutes of Health, the Public Health Service for support of this research.

[1] M. Sprinzl, J. Farkaš, and F. Šorm, *Tetrahedron Letters*, 1969, 289.
[2] E. M. Acton, K. J. Ryan, and L. Goodman, *Chem. Comm.*, 1970, 313.
[3] M. Bobek, J. Farkaš, and F. Šorm, *Tetrahedron Letters*, 1970, 4611.
[4] See, for example, (4b) later; see also ref. 1.
[5] R. K. Robins, L. B. Holum, and F. W. Furcht, *J. Org. Chem.*, 1956, 21, 833.
[6] C. P. J. Glaudemans and H. G. Fletcher, jun., *ibid.*, 1963, 28, 3004.